Seizure 20 (2011) 431–432

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Case report

Phenytoin-induced Stevens–Johnson syndrome with negative HLA-B*1502 allele in mainland China: Two cases

Fa-Yun Hu [a,b], Xin-Tong Wu [a,c], Dong-Mei An [a], Bo Yan [a], Hermann Stefan [c], Dong Zhou [a,*]

[a] Department of Neurology, West China Hospital, Sichuan University, Chengdu, Sichuan Province 610041, China
[b] Department of Neurology, Renmin Hospital, Hubei University of Medicine, Shiyan, Hubei Province 442000, China
[c] Epilepsy Center, Department of Neurology, University Hospital of Erlangen-Nuernberg, Erlangen 91054, Germany

ARTICLE INFO

Article history:
Received 5 May 2010
Received in revised form 3 November 2010
Accepted 17 January 2011

Keywords:
Phenytoin
Carbamazepine
HLA-B*1502
Stevens–Johnson syndrome
Antiepileptic drugs

ABSTRACT

Antiepileptic drugs-induced Stevens–Johnson syndrome (SJS) is a life-threatening severe cutaneous adverse reaction. Recent studies in Thailand and Taiwan showed a significant association between phenytoin (PHT)-induced SJS and human leucocyte antigen HLA-B*1502 allele. Although the US FDA had issued an alert to clinicians, insufficient information is available to recommend testing for HLA-B*1502 in Asian patients in line for PHT treatment. Therefore, extended studies are necessary to further evaluate the potential association between PHT-induced SJS and HLA-B*1502 allele in various populations. To date, no similar data exist in mainland China. Here, we describe two Chinese Han cases of PHT-induced SJS with negative HLA-B*1502 allele, in which HLA high-resolution genotyping showed two heterozygous HLA-B*4601/B*5102 and HLA-B*3701/B*4601 allele, respectively. Our findings provide evidence to support that other genetic markers or nongenetic factors could contribute to the susceptibility of PHT-induced SJS, except for HLA-B*1502 allele. Further studies are encouraged to investigate the genetic link with PHT-induced serious skin reactions in future.

1. Introduction

Carbamazepine (CBZ) and phenytoin (PHT) are among the most common causes of antiepileptic drugs (AEDs)-induced cutaneous adverse reactions.[1] Recent studies have uncovered a strong genetic association between CBZ-induced Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and human leucocyte antigen HLA-B*1502 allele in Asians.[2–7] In order to safer AEDs use, the US FDA and similar control agencies in Canada and Taiwan have updated the CBZ label to include genetic information, and recommended screening for HLA-B*1502 allele before starting CBZ treatment in Asians.[8] These significant advances in pharmacogenetic study inspired much scientific interest among researchers to detect other aromatic antiepileptic drugs, such as PHT and oxcarbazepine (OXC). Recently, a significant association of PHT-induced SJS/TEN with HLA-B*1502 allele had been observed in Thailand and Taiwan populations.[5,6] However, no pertinent data exist in mainland China until recently. In the present study, we report two Chinese Han cases of PHT-induced SJS who test negative for HLA-B*1502 allele and review the related literature.

2. Case report

2.1. Case 1

A 38-year-old Chinese woman was presented to our emergency department due to widespread skin rashes and high fever. The patient had a 5-year history of idiopathic generalized epilepsy. Sodium valproate (VPA) and CBZ (600 mg daily, respectively) were prescribed since 2004. The number of epileptic seizures was significantly reduced to about one in every one to two months. Since July 5, 2009 CBZ was withdrawn due to incomplete seizure control, and PHT (150 mg/day) was introduced into her therapy to replace CBZ. Unfortunately, moderate fever and maculopapular rashes occurred all over the cheeks and arms of the patient since September 13, 2009. Starting from September 15, 2009, her temperature reached 39.6 °C, and blisters appeared on her face. The patient was then admitted to the Department of Dermatology.

On admission, physical examination showed widespread erythematous macules and papules with blisters and detached epidermis on her face, neck, trunk, feet, and upper limbs. The estimated skin detachment was approximately 5% of body surface area. Scattered skin rashes on the lower limbs and diffuse oral ulcers were also observed. Laboratory examinations including routine blood chemistry, abdominal ultrasound scan, thyroid function, and immunological inspection were not significant abnormal. The patient was diagnosed as PHT-induced SJS. After

* Corresponding author. Tel.: +86 28 85423038; fax: +86 28 85423550.
E-mail address: zhoudong66@yahoo.de (D. Zhou).

1059-1311/$ – see front matter © 2011 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.seizure.2011.01.005

a written informed consent was obtained, genetic testing was performed by polymerase chain reaction sequencing-based typing (PCR-SBT) method. HLA high-resolution genotyping showed a heterozygous HLA-B*4601/B*5102 allele. After being treated with steroids and antihistamine for 13 days, the patient greatly improved and she was discharged.

2.2. Case 2

A 63-year-old Chinese man, with a history of hypertension and cerebral vascular accidents, was admitted to our hospital with complaints of low-grade fever and erythema. The patient had not been diagnosed with hypertension until the occurrence of intracerebral hemorrhage due to the absence of routine physical examination. Secondary epilepsy occurred six months after the surgical treatment of the left intracerebral hemorrhage. PHT (100 mg/day) was administered since the first seizure. Unfortunately, extensive skin rashes and low-grade fever appeared on the 15th day after the antiepileptic therapy. This was followed by the manifestation of blisters and oral ulcers. Physical examination showed widespread erythematous macules with blisters and target-like lesions on his cheeks, trunk, and proximal limbs. The skin detachment was approximately 2% of body surface area. Numerous oral ulcers were also observed. The remainder of his physical examination was normal. Laboratory examinations found no evidence of internal organ involvement. Clinical history and laboratory tests excluded other potential causative drugs or concomitant infections, including over-the-counter drugs, NSAID, antibiotics and HIV. The patient was diagnosed as PHT-induced SJS by two dermatologist. HLA genotyping showed a heterozygous HLA-B*3701/B*4601 allele.

3. Discussion

SJS and TEN are characterized by rapidly expanding blistering exanthema of purpuric macules and target-like lesions accompanied by mucosal involvement and skin detachment,[9] with a mortality rate that can reach up to 40%.[10] The diagnostic criteria of SJS/TEN are based on the clinical morphology. SJS is defined as skin detachment of less than 10% of body surface area, an overlap of SJS/TEN is defined as skin detachment of 10–30% and TEN is defined as skin detachment of greater than 30%.[9] In this study, the two patients met the diagnostic criteria for PHT-induced SJS according to Roujeau's classification.[9] The first case was on two antiepileptic drugs (PHT and VPA), in which VPA was continuously administrated for more than four years and no adverse drug reactions were observed. Other potential causative drugs or infections, including NSAID, antibiotics and HIV, have also been excluded. Therefore, PHT was identified as the culprit agent, although it is unusual that SJS occurred after taking the medication for over 2 months. It is worth noting that, when combined treatment with VPA, plasma concentration of PHT may have a larger change owing to competitive binding with the protein between drugs. The interactions between drugs may be partly responsible for the delayed development of SJS, but this need to be further confirmed in future.

Owing to the similar structure between PHT and CBZ, the US FDA is investigating the genetic link with PHT-induced serious skin reactions, including SJS and TEN. While insufficient information is available to recommend testing for HLA-B*1502 in Asian patients in line for PHT treatment, physicians are still advised to avoid PHT and fosphenytoin as alternatives to CBZ therapy in patients who test positive for the HLA-B*1502 allele.[11] Previous studies in Hong Kong and Thailand observed a 100% positive for HLA-B*1502 allele among patients with PHT-induced SJS.[4,5] Recent study in Taiwan also showed a significant association between PHT-induced SJS/TEN and HLA-B*1502 allele.[6] In the present study, HLA high-resolution genotyping did not detect the presence of HLA-B*1502 allele in both patients, in addition to a common HLA-B*4601 which has been confirmed as a frequent allele in Han population in Southwest China.[12] Our results indicate that HLA-B*1502 allele is not a universal marker for PHT-induced SJS, and other genetic markers or environmental factors may contribute to the genetic susceptibility of PHT-induced severe cutaneous reactions in Han Chinese. However, the failure to detect a positive HLA-B*1502 allele in patients with PHT-induced SJS should not be considered as strong evidence against the FDA's guideline due to the small sample size. Caution should be exercised for PHT no matter whether the patients carry HLA-B*1502 allele. In future, larger study should be necessary to further evaluate the potential association between PHT-induced severe cutaneous reactions and the HLA-B*1502 allele in various populations.

Acknowledgement

This study was supported by Program for Changjiang Scholars and Innovative Research Team in University of China (no. IRT0847). We would like to thank all subjects who took part in this study.

References

1. Arif H, Buchsbaum R, Weintraub D, Koyfman S, Salas-Humara C, Bazil CW, et al. Comparison and predictors of rash associated with 15 antiepileptic drugs. *Neurology* 2007;**68**:1701–9.
2. Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, et al. Medical genetics: a marker for Stevens–Johnson syndrome. *Nature* 2004;**428**:486.
3. Hung SI, Chung WH, Jee SH, Chen WC, Chang YT, Lee WR, et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. *Pharmacogenet Genomics* 2006;**16**:297–306.
4. Man CB, Kwan P, Baum L, Yu E, Lau KM, Cheng AS, et al. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. *Epilepsia* 2007;**48**:1015–8.
5. Locharernkul C, Loplumlert J, Limotai C, Korkij W, Desudchit T, Tongkobpetch S, et al. Carbamazepine and phenytoin induced Stevens–Johnson syndrome is associated with HLA-B*1502 allele in Thai population. *Epilepsia* 2008;**49**:2087–91.
6. Hung SI, Chung WH, Liu ZS, Chen CH, Hsih MS, Hui RC, et al. Common risk allele in aromatic antiepileptic-drug induced Stevens–Johnson syndrome and toxic epidermal necrolysis in Han Chinese. *Pharmacogenomics* 2010;**11**:349–56.
7. Mehta TY, Prajapati LM, Mittal B, Joshi CG, Sheth JJ, Patel DB, et al. Association of HLA-B*1502 allele and carbamazepine-induced Stevens–Johnson syndrome among Indians. *Indian J Dermatol Venereol Leprol* 2009;**75**:579–82.
8. Ferrell Jr PB, McLeod HL. Carbamazepine, HLA-B*1502 and risk of Stevens–Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. *Pharmacogenomics* 2008;**9**:1543–6.
9. Roujeau JC. The spectrum of Stevens–Johnson syndrome and toxic epidermal necrolysis: a clinical classification. *J Invest Dermatol* 1994;**102**:28S–30S.
10. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med* 1994;**331**:1272–85.
11. Kuehn BM. FDA: Epilepsy drugs may carry skin risks for Asians. *JAMA* 2008;**300**:2845.
12. Yao Y, Shi L, Shi L, Matsushita M, Yu L, Lin K, et al. Distribution of HLA-A, -B -Cw, and -DRB1 alleles and haplotypes in an isolated Han population in Southwest China. *Tissue Antigens* 2009;**73**:561–8.